REMARKS

Claims 6, 9, 10, 12 to 15, 51, and 53 are pending in the subject application. Applicants have amended claims 6, 9, 10, 12, 13, 15, 51, and 53 herein.

Support for the amendments to claims 6 and 51 may be found, *inter alia*, in the specification as originally filed at page 2, lines 14 to 18; and page 8, lines 9 to 15.

Support for the amendments to claim 9 may be found, *inter alia*, in the specification as originally filed at page 7, lines 27 to 29.

Support for the amendments to claims 10 and 13 may be found, *inter alia*, in the specification as originally filed at page 7, lines 27 to 29; page 8, lines 9 to 15; and page 14, lines 19 to 27.

Support for the amendments to claim 12 may be found, *inter alia*, in the specification as originally filed at page 2, lines 14 to 18; and page 7, lines 27 to 29.

Support for the amendments to claim 15 may be found, *inter alia*, in the specification as originally filed at page 2, lines 14 to 18; and page 12, lines 8 to 12.

Applicants also have amended claim 53 herein to correct a typographical error. Accordingly, after entry of this Supplemental Amendment, claims 6, 9, 10, 12 to 15, 51, and 53

will be pending and under examination.

The November 4, 2008 Advisory Action

The November 4, 2008 Advisory Action indicated that the October 6, 2008 Amendment has been considered but allegedly does not place the application in condition for allowance. The Examiner's specific rationale is set forth on page 2, lines 1 to 24, of the November 4, 2008 Advisory Action.

Claim Rejection Under 35 U.S.C. § 103(a) - Abstract of Strieter et al. in view of Le et al. PCT

The November 4, 2008 Advisory Action indicated that the October 6, 2008 Amendment failed to overcome the rejection of claim 6 under 35 U.S.C. § 103(a) as allegedly unpatentable over the abstract of Strieter, R.M., et al. (1993) "Role of tumor necrosis factor-α in disease states and inflammation," Crit. Care Med. 21(10 Suppl.):S447-S463 ("Abstract of Strieter et al.") in view of PCT International Application No. WO 92/16553 A1, published October 1, 1992 and naming Junming Le et al. as applicants ("Le et al. PCT"). The Examiner's specific rationale is set forth on page 2, lines 2 to 18, of the November 4, 2008 Advisory Action.

Applicants' Response

In response, without conceding the accuracy of the Examiner's position and in order to expedite prosecution, applicants have amended claim 6. Applicants maintain that the rejection

cannot be applied to claim 6, as amended herein, for at least the reasons set forth in the October 6, 2008 Amendment and set forth below.

Applicants maintain that Freedman. B.D., and Natanson, C. (1995) "Clinical trials in sepsis and septic shock in 1994 and 1995", Curr. Opin. Crit. Care 1:349-357 ("Freeman and Natanson") demonstrate a lack of predictability in the art. The Examiner asserted that "one of skill in the art would reasonabl[y] conclude that Le et al. [PCT] was teaching that the affinity of the cA2 antibody would provide for a potent neutralization or inhibition of human TNF alpha in vivo" at page 2, lines 16 to 17, of the November 4, 2008 Advisory Action.

Freeman and Natanson disclose that "[a]nti-TNF-alpha antibodies failed to show benefit in septic patients in two separate phase II (CB006, CellTech, Slough, UK; and MAK-195-F, Knoll AG, Ludwigshafen, Germany) clinical trials" at page 3, lines 56 to 57[1] and that "971 patients infused with placebo or anti-TNF-alpha antibody (Bay-X-1351, Bayer AG, subsidiary of Miles Biological Products, Berkeley, CA) showed no beneficial effects" at page 3, lines 58 to 59. Applicants note that the monoclonal antibodies used in the three clinical trials (CB006, MAK-195-F, and Bay-X-1351, respectively) are different monoclonal antibodies with different affinities. Applicants respectfully submit that the Examiner has not established that

[1] The pages numbers refer to the copy of Freeman and Natanson attached as Exhibit A to the January 16, 2008 Amendment submitted in connection with the subject application.

the advantages which the Examiner attributes to the monoclonal antibodies of Le et al. PCT would have been sufficient to produce beneficial effects in the three clinical trials. Applicants respectfully submit that in the absence of such a showing, the Examiner has failed to rebut Freeman and Natanson's disclosure of unpredictability in the art.

In view of the foregoing, applicants maintain that claim 6, as amended herein, is not obvious over Abstract of Streiter et al. in view of Le et al. PCT Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. § 103(a) - Le et al. Patent in view of Bender et al.

The November 4, 2008 Advisory Action indicated that the October 6, 2008 Amendment failed to overcome the rejection of claims 6, 9, 10, 12 to 15, and 53 under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,656,272, issued August 12, 1997 to Junming Le et al. ("Le et al. Patent") in view of U.S. Patent No. 5,317,019, issued May 31, 1994 to Paul E. Bender et al. ("Bender et al."). The Examiner's specific rationale is set forth on page 2, lines 18 to 21, of the November 4, 2008 Advisory Action.

Applicants' Response

In response, without conceding the accuracy of the Examiner's position and in order to expedite prosecution, applicants have

amended claims 6, 9, 10, 12 to 15, and 53. Applicants maintain that the rejection cannot be applied to claims 6, 9, 10, 12 to 15, and 53, as amended herein, for at least the reasons set forth in the October 6, 2008 Amendment and set forth below.

Applicants maintain that there was no reasonable basis of success of the combination of Le et al. Patent and Bender et al.

Le et al. Patent discloses the administration of anti-TNF antibodies for the treatment of TNF-related pathologies at column 33, line 54, to column 35, line 5. However, applicants note that Le et al. Patent does not disclose any of the thrombotic disorders recited in the amended claims.

Bender et al. discloses inhibiting the production of TNF by monocytes or macrophages by administering specific compounds of Formula (I) or Formula (II) at column 3, line 66, to column 4, line 13, and column 5, lines 36 to 51, respectively.

Applicants maintain that the disclosure of administration of anti-TNF antibodies of Le et al. Patent is unlike the disclosure of inhibiting the *production* of TNF by specific compounds of Bender et al. because the disclosures of Le et al. Patent and Bender et al. are directed at different stages of TNF production and activity. Therefore, one of ordinary skill in the art would have no reasonable basis of success of the combination of Le et al. Patent and Bender et al.

In view of the foregoing, applicants maintain that claims 6, 9, 10, 12 to 15, and 53, as amended herein, are not obvious over Le et al. Patent in view of Bender et al. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. § 103(a) - Le et al. Patent in view of Bender et al. and in further view of Naughton et al.

The November 4, 2008 Advisory Action indicated that the October 6, 2008 Amendment failed to overcome the rejection of claims 6, 9, 10, 12 to 15, and 53 under 35 U.S.C. § 103(a) as allegedly unpatentable over Le et al. Patent and Bender et al. as applied to claims 6, 9, 10, 12 to 15 and 53, above, and in further view of U.S. Patent No. 5,863,531, issued January 26, 1999 to Gail K. Naughton and Brian K. Naughton ("Naughton et al."). The Examiner's specific rationale is set forth on page 2, lines 21 to 24, of the November 4, 2008 Advisory Action.

Applicants' Response

In response, without conceding the accuracy of the Examiner's position and in order to expedite prosecution, applicants have amended claims 6, 9, 10, 12 to 15, and 53. Applicants maintain that the rejection cannot be applied to claims 6, 9, 10, 12 to 15, and 53, as amended herein, for at least the reasons set forth in the October 6, 2008 Amendment and set forth below.

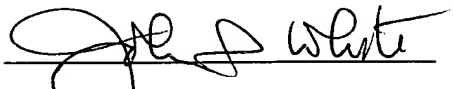
Applicants maintain that the Examiner has acknowledged that Naughton et al. does not disclose an element of the claimed invention. The Examiner indicated that "Naughton et al. is relied upon not for the identity of an idiotype of an anti-TNF antibody, but for the teachings regarding thromboembolism as a TNF-mediated disease which can be treated by anti-TNF antibodies" at page 2, lines 23 to 24, of the November 4, 2008 Advisory Action. Applicants maintain that Naughton et al. discloses at most "peptides or polypeptides corresponding to the idiotype of neutralizing antibodies for tumor necrosis factor (TNF)" at column 5, lines 10 to 13, *i.e.* the anti-TNF idiotypes and not the anti-TNF antibodies themselves. Therefore, applicants respectfully maintain that Naughton et al. does not disclose an element of the claimed invention.

In view of the foregoing, applicants maintain that claims 6, 9, 10, 12 to 15, and 53, as amended herein, are not obvious over Le et al. Patent in view of Bender et al. and in further view of Naughton et al. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $810.00 fee for a Request for Continued Examination and a $620.00 fee for a further one-month extension of time, is deemed necessary in connection with the submission of this Supplemental Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

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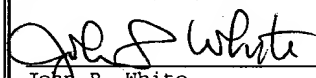

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John P. White Date
Reg. No. 28,678